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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/806,253	03/22/2004	David C. Baulcombe	616292000110	1920

25225 7590 11/25/2008

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EXAMINER	
PITRAK, JENNIFER S	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
11/25/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/806,253	BAULCOMBE ET AL.	
	Examiner	Art Unit	
	JENNIFER PITRAK	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-37,39-41,49 and 66* is/are pending in the application.

4a) Of the above claim(s) *33,34,39 and 40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32, 35, 36, 37, 41, 49, 66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *06/18/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Remarks

Applicant's amendments and arguments filed 05/09/2008 have been considered. Claim 66 was added. Claims 32-37, 39-41, 49, and 66 are pending. Claims 33, 34, 39, and 40 are withdrawn from consideration as being directed to non-elected subject matter. Claims 32, 35, 36, 37, 41, 49, and 66 are under examination.

Inventorship

In the Disclosure of Assertion of Inventorship filed on 05/09/2008, Applicant requested a response as to whether, in light of MPEP § 2137.05(I), the declaration on file is sufficient to create the presumption that the named inventors are the only inventors in the case. In response, it is noted that the declaration on file is sufficient to create the presumption that the named inventors are the only inventors in this case and no additional declaration refuting inventorship by Mr. L. Scott is necessary to establish this presumption.

Priority

Claims 32, 35, 36, 37, 49, and 66 are afforded the priority date of 10/27/1999 and claim 41 is afforded the priority date of 01/26/2000 for the reasons of record.

Claim Rejections - 35 USC § 102 - withdrawn

The amendments to the claims have obviated the rejection of claims under 35 USC § 102(e) as being anticipated by Crooke, *et al.*

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 32, 36, 37, 49, and 66 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Lee, *et al.* (1993, Cell, v.75:843-854, item 7 on 03/11/2008 IDS).

The claims are to a method of detecting post-transcriptional gene silencing of a target gene in an organism comprising detecting in a nucleic acid extract prepared from the organism in which it is suspected that PTGS is occurring the presence of short antisense RNA molecules (SARMs) or short sense RNA molecules (SSRMs) that are 20-25 nucleotides in length in the extract and determining identity or similarity of the short RNA molecules (SRMs) with the target gene.

Lee, *et al.* teach the identification of two RNAs that are suspected of regulating *lin-14* gene expression in the nematode, *C. elegans*, by an antisense mechanism (p.843. end of last paragraph). Lee, *et al.* teach the detection of post-transcriptional gene silencing of the *lin-14* gene by detecting the *lin*-4S and *lin*-4L transcripts, which have sequence similarity to the 3'UTR of the target gene, *lin*-14 (paragraph spanning pages 846-7; Figure 5 on p.846; p.848, first paragraph). The *lin*-4S transcript is approximately 22 nucleotides and is antisense to the target

region in the *lin-14* 3'UTR (Figure 8b). The *lin*-4L transcript is comprised of sense and antisense RNAs of about 25 nucleotides, each of which has sequence similarity to *lin-14* as determined by northern blot with an antisense-specific probe and subsequent sequencing, that are connected by a 7-nucleotide linker (Figure 5 and Figure 8). Detection and sequencing of the *lin*-4L transcript detects and characterizes the sense RNAs of 20-30 nucleotides. Thus, Lee, *et al.* clearly anticipate the instant claims.

Claims 32, 33, 35, 36, and 66 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Noonberg, *et al.* (1997, U.S. Patent 5,624,803).

The claims are to a method of detecting post-transcriptional gene silencing of a target gene in organisms including plants and mammals comprising detecting in a nucleic acid extract prepared from the organism in which it is suspected that PTGS is occurring the presence of short antisense RNA molecules (SARMs) that are 20-30 nucleotides in length in the extract and determining identity or similarity of the short RNA molecules (SRMs) with the target gene.

Noonberg, *et al.* teach gene-regulation and gene-therapy methods comprising the intracellular expression of antisense oligonucleotides from U6-type RNA polymerase III promoters (column 1, lines 15-27). Noonberg, *et al.* describe their system, and "in vivo oligonucleotide generator" for intracellular generation of short sequence-specific oligonucleotides for the purpose of gene regulation, which provide for a continuous and abundant supply of short genetic fragments for use in gene regulation (column 7, lines 25-32). The short antisense fragments are defined as being between 20-50 nucleotides in length (column 15, lines 1-10) and in Figure 2, the oligonucleotides are depicted as 30 nucleotides in length (Figure 2a, "oligo-1" and "oligo-2"). At column 20, lines 25-29, Noonberg, *et al.* describe that

the in vivo oligonucleotide generator can be used to create new genetically altered organisms, cells and tissues, useful in agriculture and in human and veterinary medicine. At column 13, lines 47-60, Noonberg, *et al.* teach that the oligonucleotide generators can be used to deliver oligonucleotides to any type of eukaryotic cell, such as plants and humans. Figures 5-7 show the detection of the antisense oligonucleotide in the "U6ON" transcript by northern blot. Thus, Noonberg, *et al.* clearly anticipate claims 32, 33, 35, 36, and 66.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 32, 35, 36, 37, 49, and 66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee, *et al.* (1993, Cell, v.75:843-854, item 7 on 03/11/2008 IDS).

Claims 32, 36, 37, 49, and 66 are described in the preceding rejection. Claim 35 is to the method of detecting PTGS in a mammal.

Lee, *et al.* teach the detection of PTGS in *C. elegans* by detecting SRMs with sequence similarity to the target gene as described in the preceding rejection. Lee, *et al.* do not explicitly teach the detection of PTGS in a mammal. However, the Lee reference does teach that the involvement of 3'UTR sequences in posttranscriptional regulatory mechanisms is becoming increasingly clear and that mRNAs of mouse genes, such as protamines, contain developmentally

significant posttranscriptional regulatory sequences in their 3'UTRs and that the possibility exists that such mammalian genes may be regulated by small RNAs much like the case of *lin-4* and *lin-14* (p. 851, first paragraph).

It would have been obvious to detect post-transcriptional gene silencing in an organism by detecting in a nucleic acid extract from the organism the presence of SRMs 20-30 nucleotides in length with similarity to a target gene as taught by Lee, *et al.* for the target gene, *lin-14*. It further would have been obvious to detect PTGS in a mammal, such as a mouse, because Lee, *et al.* suggest posttranscriptional regulatory sequences in the 3'UTRs of mouse genes such as protamines and that such genes may be posttranscriptionally regulated by the same type of small RNAs as for the *lin-14* gene in *C. elegans*. One of ordinary skill would immediately recognize the small RNA mediated PTGS in *C. elegans* as a likely means for PTGS in other organisms including mammals because Lee, *et al.* explicitly suggest so. One would have a reason to detect small RNAs corresponding to mouse protamine genes to determine if PTGS was occurring in mouse because Lee, *et al.* indicate that the possibility exists for small regulatory RNAs to play a role in the posttranscriptional regulation of such genes. Furthermore, those of skill in the art, biologists, are motivated to identify the conservation of biological functions among organisms and, as such, would be motivated to detect PTGS in mouse to evaluate the conservation of the small RNA-mediated regulation taught by Lee, *et al.* Therefore, the claims would have been obvious at the time of the instant invention.

Claims 32, 35, 36, 37, 41, 49, and 66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee, *et al.* (1993) as applied to claims 32, 35, 36, 37, 49, and 66 above, and further in view of Schena, *et al.* (1998, Trends in Biotechnology, v.16:301-6).

Claims 32, 35, 36, 37, 49, and 66 are described in the preceding rejection. Claim 41 is to the method of detecting PTGS in an organism wherein determining sequence similarity with the target gene is done with a library of genes from the organism.

Lee, *et al.* teach the detection of PTGS in an organism as described in the preceding rejections. Lee, *et al.* teach detection of SRMs with sequence similarity to the target gene by northern blot. Lee, *et al.* do not teach detection of SRMs with sequence similarity to the target gene by using a library of genes from the organism.

Schena, *et al.* teach the use of microarrays, which contain a library of genes from an organism, for expression profiling. At page 301, last paragraph, Schena, *et al.* teach the benefits of using microarrays over traditional hybridizations, such as northern blots, include a reduction of reagent consumption, minimization of reaction volumes, an increase of the sample concentration, and acceleration of the reaction kinetics.

It would have been obvious at the time of the invention to probe for SRMs to detect PTGS as taught by Lee, *et al.* It further would have been obvious to detect SRMs with a microarray, as taught by Schena, *et al.*, instead of with the northern blot taught by Lee, *et al.*, because Schena, *et al.* teach that microarrays provide benefits over membrane hybridization technologies (northern blots) such as saving reagents and increased sample concentration. One of skill in the art would recognize microarrays as a simple substitution of one known expression

detection technology for another. Therefore, the claims would have been obvious at the time of the instant invention.

Claims 32-36, 49, and 66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Noonberg, *et al.* (1997, U.S. Patent 5,624,803).

Claims 32, 33, 35, 36, and 66 are described above under the rejection under 35 U.S.C. § 102(b). Claim 34 is to the method of claim 32 wherein the organism is a nematode. Claim 49 is to the method of claim 32 wherein the short RNA molecules are 20-25 nucleotides in length.

Noonberg, *et al.* teach gene-regulation and gene-therapy methods comprising the intracellular expression of antisense oligonucleotides as described above under the 102(b) rejection. Noonberg, *et al.* describe the short antisense fragments as being between 20-50 nucleotides in length (column 15, lines 1-10) and in Figure 2, the oligonucleotides are depicted as 30 nucleotides in length (Figure 2a, "oligo-1" and "oligo-2"). At column 20, lines 25-29, Noonberg, *et al.* describe that the in vivo oligonucleotide generator can be used to create new genetically altered organisms, cells and tissues, useful in agriculture and in human and veterinary medicine. At column 13, lines 47-60, Noonberg, *et al.* teach that the oligonucleotide generators can be used to deliver oligonucleotides to any type of eukaryotic cell. Noonberg, *et al.* do not explicitly teach the use of the in vivo oligonucleotide generator in a nematode and Noonberg, *et al.* do not explicitly teach oligonucleotides of 20-25 nucleotides in length.

It would have been obvious to use Noonberg's method of in vivo antisense oligonucleotide expression in a nematode. Noonberg, *et al.* suggest the use of their in vivo oligonucleotide generator system for genetically altering organisms and that the system can be

used in any type of cell. Nematodes are one type of eukaryotic organism encompassed by the teachings of Noonberg, *et al.* It also would have been obvious to use Noonberg's method with oligonucleotides of between 20-25 nucleotides in length because such a range overlaps with the range of 20-30 taught by Noonberg, *et al.* Thus, claims 32-36, 49, and 66 would have been obvious at the time of the instant invention.

Claims 32-36, 41, 49, and 66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Noonberg, *et al.* (1997, 5,624,803) as applied to claims 32-36, 49, and 66 above and further in view of Schena, *et al.* (1998, Trends in Biotechnology, v.16:301-6).

Claims 32-36, 49, and 66 are described in the preceding rejection. Claim 41 is to the method of detecting PTGS in an organism wherein determining sequence similarity with the target gene is done with a library of genes from the organism.

Noonberg, *et al.* teach the detection of short antisense oligonucleotides in an organism by northern blot as described in the preceding rejections. Noonberg, *et al.* do not teach detection of oligonucleotides with a library of genes from the organism.

Schena, *et al.* teach the use of microarrays, which contain a library of genes from an organism, for expression profiling. At page 301, last paragraph, Schena, *et al.* teach the benefits of using microarrays over traditional hybridizations, such as northern blots, include a reduction of reagent consumption, minimization of reaction volumes, an increase of the sample concentration, and acceleration of the reaction kinetics.

It would have been obvious at the time of the invention to probe for short antisense oligonucleotides as taught by Noonberg, *et al.* It further would have been obvious to detect the

oligonucleotides with a microarray, as taught by Schena, *et al.*, instead of with the northern blot taught by Noonberg, *et al.*, because Schena, *et al.* teach that microarrays provide benefits over membrane hybridization technologies (northern blots) such as saving reagents and increased sample concentration. One of skill in the art would recognize microarrays as a simple substitution of one known expression detection technology for another. Therefore, the claims would have been obvious at the time of the instant invention.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JENNIFER PITRAK whose telephone number is (571)270-3061. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Pitrak
Examiner
Art Unit 1635

/JD Schultz/
Supervisory Patent Examiner, Art Unit 1635